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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
FITZGERALD, D

18M1/0516

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ART UNIT PAPER NUMBER

1812

DATE MAILED: 05/16/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8 Dec 1995 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9, 17-21, 24 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 10-16, 22, 23 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-9, 17-21, 24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified ^{copies} copy has ☒ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Applicant's amendments have obviated the objection regarding duplicative claims (¶ 8 of the Office action mailed 8 September 1995, Paper No. 9) and the rejection under § 112, second paragraph (¶ 9). The objection regarding informalities (¶ 5) and the concerns raised at ¶¶ 6 and 7 have been satisfactorily addressed.

5 Insofar as they are applicable to the rejections set forth below, applicant's arguments filed 8 December 1995 have been fully considered but they are not deemed to be persuasive.

 The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Applicant's election without traverse of group I, original claims 1-9 and 17-23, 10 in the amendment filed 8 December 1995 (Paper No. 12) is acknowledged.

3. The following technical error in Applicant's Sequence Listing was corrected by the PTO Scientific and Technical Information Center: the margins were changed to prevent "word-wrap" problems.

4. In response to points legitimately raised in applicant's arguments, the examiner has 15 reviewed the prior art and has identified references which it is believed fully address these concerns. The outstanding rejection under § 103 is withdrawn in favor of a new rejection based upon these references, as set forth below. The delay in citing the new art is regretted.

5. Claims 1-3 and 17-19 are rejected under 35 U.S.C. § 103 as being unpatentable over Miyake *et al.* (JB, 1985) in view of Chang *et al.* (US 4,963,495), further in view of 20 Vandlen *et al.* (US 5,367,060), Capon *et al.* (US 5,455,165), and Baxter *et al.* (5,258,287).

 The teachings of the Miyake reference which are relied upon, as well as the differences between this disclosure and the claimed subject matter, are set forth at ¶ 11 of Paper No. 9.

 Chang discloses expression vectors for the periplasmic expression of proteins in *E. coli* (abstract). Preferred vectors include bacterial promoters, including the *phoA* promoter, and 25 signal peptide-encoding sequences from the heat-stable enterotoxin of *E. coli* (STII). In a series of controlled experiments, an expression vector containing these components was shown to afford substantially better expression of the same protein in *E. coli* systems than did an expression cassette employing both a promoter and signal peptide sequence derived from the *phoA* (= AP) gene (Table I). Although the reference does teach that the art is somewhat empirical (see col. 30 5, lines 36-68), it nonetheless does teach that a suitable combination of promoter and signal

peptide sequence can be found with a reasonable amount of experimentation for the efficient expression of eukaryotic proteins in bacterial host cells. Chang also discloses that the STII Shine-Dalgarno sequence "is a particularly powerful ribosome binding site which contributes to yield improvements", and that it is usable with a variety of bacterial promoters including the

5 *phoA* (\equiv AP) promoter (col. 4, lines 7-12).

Each of the Vandlen, Capon, and Baxter references discloses the cloning of a mammalian protein and provides teachings as to how it may be expressed in recombinant expression systems (see the abstract of each). In particular, each of the references teaches that the STII signal peptide is a useful component of a bacterial expression vector for making the protein it discloses.

10 See Vandlen, col. 25, lines 24-29; Capon, col. 24, lines 51-58; and Baxter, col. 9, lines 17-23.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct an expression vector for IFN- α according to Miyake, replacing the *phoA* signal peptide-encoding sequence employed by that reference with the STII signal sequence, thus to make the expression cassette taught by Chang, because Chang teaches that this expression

15 cassette affords higher levels of the heterologous protein product in *E. coli* than does a cassette containing the *phoA* signal peptide sequence. It further would have been obvious to include the STII Shine-Dalgarno sequence in such a vector because Chang teaches that such sequence is a particularly powerful ribosome binding site which will contribute to improvement of the yield. Although the prior art clearly does not convey a certainty that the particular combination of this

20 expression cassette with an IFN- α gene would afford high levels of expression, the artisan would have entertained a reasonable expectation of success in successfully practicing such an expression method both because IFN- α was known in the art to be capable of periplasmic secretion in *E. coli*, as evidenced by Miyake, and because the STII leader was generally considered by those skilled in the art to be a suitable signal peptide for the bacterial expression of a wide variety of

25 eukaryotic proteins, as evidenced by Vandlen, Capon, and Baxter. Thus the claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

6. Claims 8, 9, and 20, 21, and 24 are rejected under 35 U.S.C. § 103 as being unpatentable over Miyake in view of Chang, Vandlen, Capon, and Baxter as applied to claims

30 1-3 and 17-19 above, and further in view of Hauptmann *et al.* (US 4,917,887).

Hauptmann is relied upon for the teachings discussed in the last Office action (§ 12).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the hIFN- α sequence of Miyake with the hIFN- α 2 sequence disclosed by Hauptmann in a vector incorporating the STII signal peptide sequence, as suggested by Chang, in view of Vandlen, Capon, and Baxter, because Hauptmann evidences that the IFN species it encodes was known in the art to be useful. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

7. Claims 4-7 are rejected under 35 U.S.C. § 103 as being unpatentable over Miyake in view of Chang, Vandlen, Capon, and Baxter as applied to claims 1-3 and 17-19 above, and further in view of Protasi *et al.* (US 5,066,786) and Higashi *et al.* (US 4,828,990).

Protasi and Higashi are relied upon for the teachings discussed in the last Office action (§ 14).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to purify rhIFN- α produced according to the suggestion of Miyake and Chang as taken in view of Vandlen, Capon, and Baxter, by any methods known in the art for the purification of IFNs, including adsorption on a silecious material as suggested by Protasi or anion exchange, cation exchange, or hydrophobic interaction (phenyl) chromatography, as suggested by Higashi, because these techniques were known to be useful in the purification of recombinantly produced IFNs. It would have been *prima facie* obvious to employ any commercial available matrices known to be useful in these procedures, *e.g.*, silica gel and phenyl-, sulfopropyl-, and DEAE--SephroseTM or SephadexTM. The artisan would have expected that these techniques, optionally in combination with any other known methods for the purification of IFN- α , would have afforded a purified, active product. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

Telephone	(703) 308-3934
Fax - Art Unit 1812	(703) 308-0294
Internet	dfitz@uspto.gov

Examiner Fitzgerald is generally available Mondays through Thursdays from 8 a.m. to 5 p.m. (Eastern), and during the same hours on alternate Fridays. If he is not available to take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, his supervisor, Garnette D. Draper, may be reached at (703) 308-4232.

Official papers may be submitted to Group 1800 by fax; see 37 C.F.R. § 1.6 and the notice published at 1096 OG 30. Submission of a confirmation copy through the mailroom is **discouraged** since entry of two copies of the same paper will tend to confuse the record.

Faxes which require special handling should be clearly labeled on the cover page, for example, "AFTER-FINAL" or "COURTESY COPY". It is also a good idea to call the Examiner when an urgent communication is faxed so that he knows to expect it. PTO fax machines are loaded with 8½ × 11 paper; faxes from legal or A4 size originals may not print out properly.

The Examiner checks his e-mail messages at least every morning. Please note that Internet e-mail is NOT considered to be secure. There is at present no procedure which allows for the submission of formal communications to the PTO by e-mail.

Inquiries of a general nature should be directed to the Group 1800 receptionist at (703) 308-0196.



DAVID L. FITZGERALD
PATENT EXAMINER
GROUP 1800

13 May 1996